UNITED STATES DEPARTMENT OF COMMERCE
**United States Patent and Trademark Office**
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/760,379 | 01/16/01 | RAUTH H | 100564-09055 |

HM12/1001
ARENT FOX KINTNER PLOTKIN & KAHN PLLC
SUITE 600
1050 CONNECTICUT AVENUE, N.W.
WASHINGTON DC 20036-5339

| EXAMINER | |
|---|---|
| KAM, C | |
| **ART UNIT** | **PAPER NUMBER** |
| 1653 | 5 |

**DATE MAILED:** 10/01/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/760,379 | Applicant(s) RAUTH ET AL. | |
|---|---|---|---|
| | Examiner Chih-Min Kam | Art Unit 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-15 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of isolation and/or purification of a proteinaceous material comprising the steps of providing an aqueous protein solution, contacting the protein solution with a hydrophobic interaction chromatography gel or with a magnetically responsive polymer particles coated with hydrophobic agarose particles, and separating off other components, does not reasonably provide enablement for a process of isolation and/or purification of a proteinaceous material comprising the steps of providing an aqueous protein solution, contacting the protein solution with any solid phase comprising a mixture of hydrophobic and hydrophilic groups on the surface and separating off other components, and at least one purification step being automated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-15 encompass a process for isolation and/or purification of a proteinaceous material comprising providing an aqueous protein solution, contacting the protein solution with solid phase containing hydrophobic and hydrophilic groups on the surface and separating off other sample components (claims 1-3 and 6-11), the process using magnetic solid particles (claim 4), the process further comprising a step of eluting the proteinaceous material from the

solid phase (claim 12) and the solid phase can be separated by magnetic means (claim13), the process wherein the purified protein is analyzed by mass spectrometry (claim 14), and the process has at least one step automated (claim 15). The specification, however, only discloses cursory conclusions (page 2, third paragraph; page 10, first paragraph), which states that a process for isolation and/or purification of a proteinaceous material comprising providing an aqueous protein solution, contacting the protein solution with a solid phase containing hydrophobic and hydrophilic groups on the surface and separating off other sample components, and the process step can be automated. There are no indicia that the present application enables the full scope in view of a process for isolation and/or purification of a proteinaceous material using the solid phase discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how these problems are resolved. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the amount of direction or guidance presented and the amount of experimentation necessary as discussed below.

(1). The amount of direction or guidance presented and the quantity of experimentation necessary.

The specification has indicated the solid particles with a diameter of 1 nm to 1 mm and having both hydrophobic and hydrophilic groups on the surface can prevent agglutination of small particles and the mobiles particles can be used in aqueous solution for purification of proteins without necessity to pack them or fix them on a support material (page 4, lines 8-25). Different solid phase materials such as silica, polystyrene or a magnetic or magnetizable

material, in particulate gamma-iron oxide coated with particles having hydrophobic and hydrophilic groups on the surface can be used as solid particles for purification (page 4, line 27-page 8, line 9). However, there is no information regarding the identity of the protein purified, the buffer used, the yield of recovery and the purity of protein after the purification procedure using the solid particles. The specification has not demonstrated how gamma-iron oxide is coated with particles of polysilicic acid or monosaccharide containing hydrophobic groups, the outcome of the purification process using the solid particles with a diameter from 1 nm to 10 mm would indicate the purification is efficient, and the automation is carried out in one of the purification steps. Therefore, the one skilled in the art would need additional infromation on the preparation of solid particles, the purification conditions and the automation for the purification procedure and further experimention is also required to assess the efficiency of the purification procedure. Since it is not routine in the art to engage in *de novo* experimentation where the expectation of success is unpredictable, the skilled artisan would require additional guidance in order to make and use such solid particles for purifying proteinaceous materials. Without such guidance, the experimentation left to those skilled in the art is undue because the amount of guidance is minimal regarding the purification procedure (see above) which leads to the requirement of further experimentation to purify a proteinaceous material.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-15 are indefinite because they lack essential steps as claimed in the process of isolation and/or purification of a proteinaceous material. The omitted steps are: the elution of the proteinaceous material from the solid phase and a step whereby the outcome of isolation and/or purification such as yield of recovery and purity of the protein can be determined. Claims 2-15 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

3. Claims 1-15 are indefinite because of the use of the term "and/or". The term "and/or" renders the claim indefinite, it is unclear in the claim whether the purification is included in the process. Claims 2-15 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend. The same type of rejection is applied in claims 5, 6 and 14.

4. Claims 1-15 are indefinite because of the use of the term "at least one surface". The term "at least one surface" renders the claim indefinite, it is unclear how many surfaces a mixture of hydrophobic and hydrophilic groups is on. Claims 2-15 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

5. Claim 7 is indefinite because of the use of the term "and mixtures thereof". Note that Markush groups must be closed and "and mixtures thereof" is open language in regard to the amounts of each in the mixtures.

6. Claim 10 recites the limitation "wherein step (c) is performed by magnetic means" in lines 1 and 2. There is insufficient antecedent basis for this limitation in claim 1.

7. Claim 11 is indefinite because of the use of the term "at least one washing step". The term "at least one washing step" renders the claim indefinite, it is unclear how many washing steps are intended.

8. Claim 13 recites the limitation "using magnetic means" in lines 2 and 3. There is insufficient antecedent basis for this limitation in claim 12.

9. Claims 10 and 13 are indefinite because of the use of the term "magnetic means". The term "magnetic means" renders the claim indefinite, it is unclear what the term "magnetic means" means.

10. Claim 11 is indefinite because of the use of the term "at least one process step is automated". The term "at least one process step is automated" renders the claim indefinite, it is unclear how many process steps are intended to be automated.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-3, 6, 8, 11, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Belew *et al.* (J. Chromatography A, 679, 67-83 (1994)).

Belew *et al.* teach a glycoprotein, recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) from inclusion bodies produced by transformed E. coli cells is purified to homogeneity by a three-step chromatographic procedure using hydrophobic interaction chromatography (HIC) as the first step. In the HIC, Phenyl Sepharose 6 FF (high sub) which has average particle size of 90 μm and are agarose beads (containing hydroxyl group) derivatized with phenyl group is used as packing material for column. The rhGM-CSF sample is dissolved in ammonium sulfate solution, applied to the HIC column, eluted the DNA contaminant with sodium phosphate-ammonium sulfate solution, and subsequently the bound protein is eluted with sodium phosphate (page 70, left column; page 74; Fig. 1), which meets the criteria of claims 1-3, 6, 8, 11, and 12. The purified rhGM-CSF is analyzed by electrospray or laser desorption mass spectrometry (page 72), which meets the criteria of claim 14.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claims 1-3, 6, 7, 8, 11 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Smeds (U. S. Patent 6,005,082).

Smeds teaches recombinant coagulation factor VIII is purified by loading an aqueous solution containing factor VIII onto a hydrophobic interaction chromatography gel, which has aromatic or aliphatic group such as octyl or butyl on agarose matrices. For example, Butyl Sepharose 4 FF which has average particle size of 90 μm and are agarose beads (containing hydroxyl group) derivatized with butyl group is used as packing material for column. The factor VIII solution is loaded onto the HIC column for adsorbing factor VIII to the gel surface, and the bound factor VIII is then eluted with buffer (column 4, line 49-column 5, line 37; column 6, lines 52-65; Examples), which meets the criteria of claims 1-3, 6, 7, 8, 11 and 12.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang *et al.* (U. S Patent 5,283,079) taken with Belew *et al.* (J. Chromatography A, 679, 67-83 (1994)) or Smeds (U. S. Patent 6,005,082).

Wang *et al.* teach magnetically responsive fluorescent polymer particles comprising polymeric core particles (1 to 100 microns) coated evenly with a layer of polymer containing magnetically responsive metal oxide and the surface of magnetically responsive polymer particles can be coated further with another layer of functionalized polymer and used as solid phase for affinity purification (column 3, lines 30-43; column 6, lines 33-64). However, Wang *et al.* do not teach using magnetic polymer particles further coated with particles comprising a

mixture of hydrophobic groups and hydrophilic groups and a process for purification proteinaceous materials. Belew *et al.* teach a glycoprotein, rhGM-CSF is purified by hydrophobic interaction chromatography (HIC) using a Phenyl Sepharose 6 FF (high sub) gel (page 70, left column; page 74; Fig. 1), and Smeds teaches recombinant coagulation factor VIII is purified by loading an aqueous solution containing factor VIII onto a hydrophobic interaction chromatography gel having octyl or butyl group on agarose matrices. At the time of invention was made, it would have been obvious to one of ordinary skill in the art to use magnetically responsive fluorescent polymer particles further coated with Phenyl Sepharose 6 FF (high sub) particles or agarose matrices with octyl group to purify the protein because the procedure would simplify the purification procedure of proteins. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

***Conclusion***

14. No claims are allowed.

Regarding the particle size and structural information of Phenyl Sepharose 6 FF gel (high sub) and Butyl Sepharose 4 FF gel of 90 μm are shown in the Pharmacia Biotech catalog (1997), pages 231 and 233.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers

for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D.
Patent Examiner

***
September 25, 2001

Chris Low Rev S.J. Low
CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600